REMARKS

The Office Action dated June 28, 2006 has been reviewed and the comments of the U.S. Patent and Trademark Office have been considered. The following remarks are respectfully submitted to place the application in condition for allowance.

A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier. Claims 1-26, 29-33 and 39-47 were previously canceled. Claims 27-28, 34-38, 48-55, 58, 61 and 64 are presently canceled. Claims 56-57, 59-60 and 62-63 have been amended. Support for the amendments may be found, for example, at least in the following sections of the original disclosure: page 1, line 6; page 7, line 15; page 8, line 13 and line 21; page 15, lines 14-23; page 16, lines 26-29; page 19, line 20; page 34, lines 14-15. New claims 65-107 have been added. Support for the new claims may be found, for example, in at least the following sections of the original disclosure: page 1, lines 4-6; page 6, lines 15-19; page 7, lines 11-13; page 7, line 17-18; page 10, lines 10-11; page 15, lines 25028; page 15, line 30 – page 16, line 8; page 16, line 8; page 18, lines 15-24; page 19, lines 19-23 and line 30; page 20, lines 10-16; page 20, line 29 – page 21, line 2; page 22, lines 23-24; page 26, lines 21-27; page 28, lines 12-15; page 29, lines 19-21; page 30, lines 20-23; page 31, line 24; page 32, lines 13-17; page 34, lines 18-20. Claims 56-57, 59-60, 52-63 and 65-107 are currently pending in this application.

Priority

The Examiner states that the prior filed application (US Application No. 09/100,812) fails to provide adequate support or enablement for claims 59 and 60. Specifically, the Examiner states that there is no written support for the limitation "a gene sequence 20 to 30

nucleotides long". The currently amended claims no longer recite the language objected to by the Examiner. Independent claim 56 has been amended to recite a synthetic genetic construct for us in a eukaryotic cell, comprising two copies of a structural gene sequence placed operably under control of a single promoter and a transcription termination sequence, having greater than 20 consecutive nucleotides identical in sequence to greater than 20 consecutive nucleotides of the target, wherein the two copies are spatially separated by a stuffer fragment. Independent claim 57 has been amended to recite a synthetic genetic construct for us in a plant cell, comprising two copies of a structural gene sequence, each copy being placed under the control of a promoter and a transcription termination sequence, having greater than 20 consecutive nucleotides identical in sequence to greater than 20 consecutive nucleotides of the target, wherein the two copies are spatially separated by a stuffer fragment. These amendments are fully supported in the priority document, specifically at page 7, line 15; page 8 line 13; page 8 line 21; page 15 lines 14-23; page 16 lines 26-29; page 34 lines 14-15. Withdrawal of the rejection is respectfully requested.

The Examiner states that claim 34 does not have written support in the priority document for the limitation "the target gene is a α-1,3-galactosyltransferase." Claim 34 has been canceled, thus making the rejection with respect to that claim moot. Applicants respectfully request withdrawal of the rejection.

The Examiner states that the claims do not have written support for the limitation "target gene is derived from the genome of a pathogen of the human cell or the genome of the human cell". The current claims have been amended to delete this limitation. Withdrawal of the rejection is respectfully requested.

Information Disclosure Statement

The Examiner states that Exhibits A and B included with the Information Disclosure Statement filed on February 11, 2005 have not been considered because the Statement fails to comply with 37 CFR 1.98(a)(2).

Exhibits A and B were submitted by an adverse party during the litigation of the related patent. Applicants are submitting these Exhibits in order to completely comply with their ethical duty to disclose all information to the US Patent and Trademark Office. Applicants point out that the lists consist of the full and complete set of material made known to Applicants as submitted by the aforesaid adverse party in the litigation. Applicants submit concurrently an Information Disclosure Statement and Form SB-08 listing the Exhibits. This IDS fully complies with 37 CFR 1.98(a)(2).

Rejections Under 35 U.S.C. § 112

The Examiner states that there is no support for new Claims 48-64, added in the Response and Amendment filed December 7, 2004. Claims 48-55, 58, 61 and 64 have been canceled, thus making the rejection with respect to those claims moot. Amended claims 56, 57, 59, 60, 62 and 63 are fully supported in the specification as discussed above, specifically at page 7, line 15; page 8 line 13; page 8 line 21; page 15 lines 14-23; page 16 lines 26-29; page 34 lines 14-15. Newly added claims 65-107 are fully supported in the specification as discussed above, specifically at page 1, lines 4-6; page 6, lines 15-19; page 7, lines 11-13; page 7, line 17-18; page 10, lines 10-11; page 15, lines 25028; page 15, line 30 – page 16, line 8; page 16, line 8; page 18, lines 15-24; page 19, lines 19-23 and line 30; page 20, lines 10-16; page 20, line 29 – page 21, line 2; page 22, lines 23-24; page 26, lines 21-27; page 28, lines 12-15; page 29, lines 19-21;

page 30, lines 20-23; page 31, line 24; page 32, lines 13-17; page 34, lines 18-20. Applicants respectfully request withdrawal of the rejection.

Claims 27, 28, 34-38, 48-51 and 53-64 are rejected under U.S.C. § 112 as failing to comply with the written description requirement. The Examiner states that claims are readable on a genus of structural gene sequence comprising a nucleotide sequence which is at least 80% identical to the sequence of the target gene. The Examiner contends that the region of the structural gene sequence is not specifically claimed so far as biochemical or molecular structure. The Examiner concludes that there is too much variation among the species of the claimed genus and there is no disclosure as to make a representative number of the disclosed species.

Applicants' respectfully traverse the rejection. Claims 27, 28, 34-38, 48-51 and 53-55, 58, 61 and 64 have been canceled, thus making the rejection with respect to those claims moot. Newly amended claims 56 and 57 no longer recite the limitation of "at least 80% identical to the sequence of the target gene". The limitations of independent claims 56 and 57 and the claims depending from them are fully supported in the specification, in at least the portions listed above, specifically at page 7, line 15; page 8 line 13; page 8 line 21; page 15 lines 14-23; page 16 lines 26-29; page 34 lines 14-15. Withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. § 102

Claims 27, 28, 36-38, 49-53, 55 and 56-61 are rejected under 35 U.S.C. § 102 as being anticipated by Dorer *et al.* The Examiner states that Dorer *et al.* teach a synthetic gene comprising a dispersed nucleic acid molecule comprising tandem copies of a nucleic acid sequence under control of a promoter sequence. The Examiner also contends the synthetic gene comprises tandem inverted and/or direct repeats of a genetic sequence which is endogenous to the genome of an animal cell operably linked to a spatially separate promoter.

Applicants respectfully traverse the rejection. Claims 27, 28, 36-38, 49-53 and 55 have been canceled, thus making the rejection with respect to those claims moot. Independent claims 56 and 57 have been amended as outlined above. Dorer *et al.* does not teach every element of Applicants' currently amended claims.

Specifically, Dorer *et al.* does not teach two copies of the structural gene sequence placed operably under the control of a single promoter sequence and a transcription termination sequence. Nor does Dorer *et al.* teach two copies of the structural gene sequence each placed operably under the control of a promoter sequence and a transcription termination sequence wherein the structural gene sequence has greater than 20 consecutive nucleotides identical in sequence to greater than 20 consecutive nucleotides of a target gene in a plant cell. The Examiner points to Figure 3 as evidence that Dorer *et al.* teach the limitations of the present invention. Close examination of Figure 3, however, indicates that the genetic arrangement of Dorer *et al.* does not contain all of the elements of the presently claimed invention. In fact, promoters are not shown in Figure 3. Figure 3, and the remainder of Dorer *et al.*, has no teaching or suggestion of a stuffer fragment which is spatially separating two copies of a structural gene sequence operably under the control of a single promoter, one copy of which is in the sense orientation and the other in the antisense orientation With regard to independent claim 57, Dorer *et al.* does not show use of a synthetic gene to reduce expression of the target gene in a plant cell. Clearly, Dorer *et al.* does not teach each and every element or the arrangement of those elements as recited in the claims and does not anticipate Applicants presently claimed invention.

The claims which are dependent on claims 56 and 57 and the newly added claims incorporate all of the limitations of the independent claims and are therefore not anticipated by

Dorer *et al.* The dependent claims recite further features which are not taught or suggested by Dorer *et al.* Withdrawal of the rejection is respectfully requested.

Claims 27, 28, 38, 49-53 and 59-64 are rejected under 35 U.S.C. § 102(e) as being anticipated by Fire *et al.* (U.S. Patent No. 6,506,559). The Examiner states that Fire *et al.* teaches a vector comprising a promoter operably linked to a nucleotide sequence with a sense strand and an antisense strand of the target gene. The Examiner characterizes the promoter as a T7 or T3 promoter, and the nucleotide sequence being at least 25 or 50 bases.

Applicants traverse the rejection. Claims 27, 28, 49-53, 61 and 64 have been canceled, thus making the rejection with respect to those claims moot. Claims 56 and 57 have been amended and new claims 65-107 added to recite a synthetic construct having a particular configuration of elements. Claim 56 has been amended to recite a synthetic genetic construct for use in a eukaryotic cell, comprising two copies of a structural gene sequence placed operably under control of a single promoter and a transcription termination sequence, each copy having greater than 20 consecutive nucleotides identical in sequence to greater than 20 consecutive nucleotides of the target, wherein the two copies are spatially separated by a stuffer fragment. Independent claim 57 has been amended to recite a synthetic genetic construct for use in a plant cell, comprising two copies of a structural gene sequence, each copy being placed under the control of a promoter and a transcription termination sequence, having greater than 20 consecutive nucleotides identical in sequence to greater than 20 consecutive nucleotides of the target gene of the plant cell, wherein the two copies are spatially separated by a stuffer fragment. Fire *et al.* neither teach nor contemplate the use of a stuffer fragment to spatially separate two copies of the structural gene, or a stuffer fragment in the particular position as now claimed. Moreover, Fire *et al.* do not disclose the length limitation of 20 nucleotides for the structural gene sequence. With regards to claim 57, Fire *et al.* does not describe a synthetic construct

capable for reducing the expression of a target gene in a plant cell, wherein two copies of the structural gene sequence are each placed operably under the control of a promoter sequence and a transcription termination sequence, each structural gene sequence having greater than 20 consecutive nucleotides identical in sequence to greater than 20 consecutive nucleotides of a target gene in a plant cell, the copies being spatially separated by a stuffer fragment. Fire *et al.* does not teach each and every element or the arrangement of those elements as recited in the claims and therefore does not anticipate Applicants presently claimed invention.

The claims which are dependent on claims 56 and 57 including the newly added claims incorporate all of the limitations of the independent claims. These claims are also not anticipated by Fire *et al.* for the reasons described above. Moreover, they recite further features which are not taught or suggested by Fire *et al.* Withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 57 and 59-64 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Fire *et al.* taken with Conrad (U.S. Patent No. 6,054,299). The Examiner states that Fire *et al.* teaches a construct comprising a promoter operably linked to a nucleotide sequence comprising a sense strand and an antisense strand of the target gene. The structural gene may comprise one or more strands of the nucleotide sequence. The Examiner states that Fire *et al.* does not teach a construct comprising one promoter operably linked to a nucleotide sequence comprising the sense strand and another promoter operably linked to a nucleotide encoding the antisense strand. The Examiner then concludes that because Conrad teaches vectors utilizing T7 and T3 promoters, it would have been obvious to combine the teachings of the two references to result in the present invention—a vector comprising one promoter operably linked to a nucleotide

encoding the sense strand and another promoter operably linked to another promoter encoding the antisense strand.

In raising an obviousness rejection under 35 U.S.C. §103, the Examiner has the burden of establishing that at the time of the invention, there was: (1) some suggestion or motivation to modify the reference or to combine reference teachings; (2) a reasonable expectation of success; and (3) that the prior art references, when combined, taught or suggested all the claim limitations. See MPEP §2143 (Aug. 2001, Latest Revision August 2005); See also In re Royka, 490 F.2d 981, 985 (C.C.P.A. 1974). Obviousness may not be established based upon hindsight or the teachings or suggestions of the inventor. W. L. Gore & Assocs., Inc. v. Garlock, Inc., 721 F.2d. 1540, 1551, 1553 (Fed. Cir. 1983); Ruiz v. A. B. Chance Co., 357 F.3d 1270, 1276 (Fed. Cir. 2004). Here, the Examiner has not met this burden. It is respectfully submitted that the obviousness rejection fails on each of the three grounds, as detailed below.

Claims 61 and 64 have been canceled, thus making the rejection with respect to those claims moot. Claim 57 has been amended to recite a synthetic genetic construct for use in a plant cell, comprising two copies of a structural gene sequence, each copy being placed under the control of a promoter and a transcription termination sequence, having greater than 20 consecutive nucleotides identical in sequence to greater than 20 consecutive nucleotides of a target gene in a plant cell, wherein the two copies are spatially separated by a stuffer fragment. Dependent claims 59, 60, 62 and 63 necessarily contain all of the limitations of claim 57.

Applicants respectfully point out that Fire *et al.* does not teach all of the limitations of amended claim 57, specifically the elements of the length limitation of 20 consecutive nucleotides identical in sequence to 20 consecutive nucleotides of a plant gene, or the stuffer fragment which spatially separates the two copies of the structural gene. Additionally, Fire *et al.*

does not contemplate the combination of these elements for reducing the expression of a target gene in a plant cell.

The deficiencies of Fire *et al.* are not cured by Conrad. Conrad is clearly non-analogous art. Conrad describes stem-loop cloning vectors for cloning a target nucleic acid sequence flanked by inverted repeat sequences, where the inverted repeat sequences form a stable stem-loop structure with the target sequence forming the loop (Col. 1, ll. 49-56). The stem loop structures only form from a single-stranded nucleic acid molecule and Conrad describes, as a required element, that the vectors produce not RNA, but single-stranded DNA. It is an essential feature of the Conrad vectors that the stem-loop structures are formed after single-stranded DNA conversion (Col. 1, ll. 23-41), for example through use of filamentous phage DNA replication control elements, see Col 3, ll. 29-49. Furthermore, the vectors necessarily comprise a fully functional replicon to allow replication of the vector.

The vectors of Conrad therefore are designed to produce a single-stranded sense or antisense molecule, but cannot produce a target-specific double-stranded RNA molecule. The vectors of Conrad are useful to produce, for example, single-stranded DNA probes which do not include the DNA sequences of the vector (Col. 1, ll. 31-41).

There is no suggestion or teaching in Conrad that the vectors could be used in gene silencing. Indeed, Conrad is entirely irrelevant to the field of gene silencing. It is clear, therefore, that Conrad and Fire *et al.* are not analogous art. The skilled person would have no motivation to combine Conrad and Fire *et al.*, or even to search Conrad for any improvements to the method of Fire *et al.* The documents are completely unrelated and it is only improper hindsight reconstruction using Applicants' own specification that leads to the Examiner's conclusion.

There is no teaching or suggestion in Conrad of a stuffer fragment which spatially separate two copies of the structural gene sequence. Conrad clearly does not add this element, missing from Fire *et al.*, as recited in Applicants' presently amended claims

In addition, and as acknowledged by the Examiner at page 11 of the Office Action date June 28, 2006, Conrad utilizes T3 or T7 promoters. These are bacteriophage (prokaryotic) promoters used in in vitro transcription assays. Conrad neither teaches nor suggests the use of eukaryotic promoters for gene silencing in plant cells, as is taught in the instant application.

Even if the references were combined (as Applicants strongly oppose), the combination would in fact lead away from the presently claimed invention. Conrad teaches the production of a single-stranded form of the target gene sequence, corresponding to the loop of the stem-loop structure. Col. 1, ll 53-56 read: "said inverted tandem repeat forming a stable secondary structure stem-loop with said target sequence being located in the loop thereof." (emphasis added). This is also clear from Figure 4 of Conrad.

The addition of Conrad would therefore inevitably lead the skilled person to produce a single-stranded form of the target gene, either an antisense strand or a sense strand depending on the orientation of the PCR insert in the vector, for use in gene silencing in animal cells as taught by Fire *et al.* This clearly leads away from the present invention, and would not provide any expectation of success.

In addition, the Examiner's attempt to pick-and-choose certain disparate elements from the many found in Conrad is improper. As such, the grounds for rejection are clearly based upon an impermissible hindsight reconstruction of the prior art teachings. Only using improper hindsight and the Applicants' disclosure as a blueprint could a practitioner arrive at the claimed invention. Such hindsight reconstruction is inappropriate.

The PTO defines one of ordinary skill in the art as one "who thinks along the lines of conventional wisdom in the art and is not one who undertakes to innovate, whether by patient, and often expensive, systemic research or by extraordinary insights, it makes no difference which." Ex parte Anderson, 21 U.S.P.Q.2d. 1241, 1256 (B.P.A.I 1991). For the reasons set forth above, an artisan thinking along the line of conventional wisdom would not have been motivated to modify the Fire *et al.* reference with Conrad as the Examiner suggests, nor would an artisan of ordinary skill have a reasonable expectation of success.

Applicants also point out that the dependent claims contain additional features which are neither taught nor suggested by Fire et al, or Conrad.

Applicants respectfully request withdrawal of the rejection.

Claims 56 and 58-64 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Fire *et al.* taken with Ladner *et al.* (U.S. Patent Application No. 5,198,346). The Examiner states that Fire *et al.* teaches a construct comprising a promoter operably linked to a nucleotide sequence comprising a sense strand and an antisense strand of the target gene. The Examiner states that Fire *et al.* does not teach the stuffer sequence. The Examiner then contends that Ladner teaches the use of a stuffer fragment having about 10 nucleotides to introduce a stop codon or a unique restriction site. The Examiner therefore concludes that it would have been obvious to combine the reference of Fire *et al.* and Ladner to result in Applicants' invention.

The rejection is respectfully traversed. Claims 58, 61 and 64 have been canceled, thus making the rejection with respect to those claims moot. Claim 56 has been amended to recite a synthetic genetic construct for use in a eukaryotic cell, comprising two copies of a structural gene sequence placed operably under control of a single promoter and a transcription termination sequence, each copy having greater than 20 consecutive nucleotides identical in

sequence to greater than 20 consecutive nucleotides of the target gene, wherein the two copies are spatially separated by a stuffer fragment.

Applicants again respectfully point out that Fire *et al.* does not teach all of the limitations of amended claim 56, specifically the elements of the length limitation of 20 consecutive nucleotides identical in sequence to 20 consecutive nucleotides of a target gene, or the stuffer fragment which spatially separates the two copies of the structural gene sequence.

The deficiencies of Fire *et al.* are not cured by Ladner. The Examiner claims that the "stuffer fragment" described in Ladner at Table 704 cures the deficiencies of Fire *et al.* The Examiner states that the "stuffer fragment" described in Ladner is used "to introduce a stop codon or a unique restriction site". In response, it is respectfully pointed out that the linker sequence of Ladner, Table 704, does not correspond to the limitation recited in amended claim 56, namely a stuffer fragment in a particular location between two copies of a structural gene sequence. There is no teaching in Ladner of a linker that spatially separates two copies of a structural gene sequence, one copy being in the sense orientation and the second being in an antisense orientation, both operably under the control of a single promoter and transcription termination sequence that is active in a eukaryotic cell. Ladner does not provide this element, missing from Fire *et al.*, as recited in Applicants' presently amended claims.

Furthermore, Ladner does not provide the length limitation recited in claim 56, also missing in Fire *et al.*, or the combination of these elements as recited in claim 56. Applicants also point out that the dependent claims contain additional features which are neither taught nor suggested by Fire *et al.*, or Ladner.

It is also respectfully submitted that Fire *et al.* and Ladner are non-analogous art and the skilled artisan would have no motivation to combine these references. These two references are about entirely unrelated fields. Ladner itself describes its "Field of (the) Invention" as:

"This invention relates to the development of novel DNA-binding proteins and polypeptides by an iterative process of mutation, expression, selection, and amplification." (Col 1, lines 41-44).

Ladner describes the generation of DNA-binding proteins obtained by variation of genes producing known binding proteins, and production and selection of these proteins in prokaryotic cells. The DNA binding proteins are produced in E. coli recA- strains. Col. 28, ll. 38-46. Ladner does not contemplate gene silencing in eukaryotic cells, as taught by Applicants' presently claimed invention. Indeed, if anything, Ladner is about production (overexpression) of DNA-binding proteins, not down-regulation of gene expression. Furthermore, Ladner is about production of proteins in prokaryotic cells, not about eukaryotic cells. Therefore, Ladner and Fire *et al.* are clearly not analogous art. There is no motivation at all for one of skill in the art to combine the teachings of Ladner and Fire *et al.*

In addition, the Examiner's attempt to pick-and-choose one particular, obscure element (even if that element would have corresponded to the limitation of claim 56) from the many found in Ladner is improper. As such, the grounds for rejection are clearly based upon an impermissible hindsight reconstruction of the prior art teachings. Only using improper hindsight and the Applicants' disclosure as a blueprint could a practitioner arrive at the claimed invention. Such hindsight reconstruction is inappropriate.

Withdrawal of the rejection is respectfully requested.

Claims 27, 34 and 35 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Fire *et al.* and D'Piece *et al.* (U.S. Patent No. 6,849,448). The Examiner characterizes Fire *et al.* as above, and in addition states that Fire *et al.* does not teach a construct comprising a structural gene comprising a nucleotide sequence which is substantially identical to the sequence of the target gene, wherein the target gene is alpha 1,3-galactosyltransferase. The Examiner states that

D'Piece *et al.* cures Fire *et al.* because it mentions the enzyme alpha-1,3 galactosyltranserase in the abstract.

Applicants respectfully traverse the rejection. However, to expedite prosecution of the present application, claims 27, 34 and 35 have been canceled, thus making the rejection moot. Withdrawal of the rejection is respectfully requested.

Claims 27 and 34-36 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Fire *et al.* taken with D'Apice *et al.* and in further view of Draper *et al.* (U.S. Patent No. 5,496,698). Fire *et al.* and D'Apice et al are characterized as above. The Examiner states that Fire *et al.* taken with D'Apice *et al.* does not specifically teach a CMV promoter. However, the Examiner concludes that the CMV promoter was well known in the art as exemplified by Draper.

Applicants respectfully traverse the rejection. To further prosecution of the application, claims 27 and 34-36 have been canceled, thus making the rejection moot. Withdrawal of the rejection is respectfully traversed.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Applicants submit concurrently a request for extension of time under 37 C.F.R. 1.136 and the accompanying fee. In the event that any additional extensions of time are necessary to prevent the abandonment of this patent application, then such extension of time are hereby petitioned. The U.S. Patent and Trademark Office is hereby authorized to charge any fees that may be required in conjunction with this submission to Deposit Account Number 50-2228, referencing matter number 025122.0101P3US (previously 023004.0104P3US) from which the undersigned is authorized to draw.

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Respectfully submitted, #55340

By _____

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